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Review Article

# Periodic limb movements during sleep and their effect on the cardiovascular system: is there a final answer?

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ABSTRACT

Periodic limb movements during sleep (PLMS) is a sleep-related movement disorder characterized by repetitive limb movements during sleep, seen predominantly in the legs but also occasionally involving the arms. These movements may be associated with arousals that can lead to increases in sympathetic tone, resulting in tachycardia and elevated systolic blood pressure. Chronic sustained tachycardia and elevated systolic blood pressure are known to be associated with the development of arrhythmias, hypertension, left ventricular hypertrophy, and congestive heart failure. However, the data are not entirely clear on whether untreated PLMS is associated with these cardiovascular risks. This review examines the current evidence on whether PLMS has any effect on the cardiovascular system.



## 1. Introduction

Periodic limb movements during sleep (PLMS) are characterized by periodic, repetitive, highly stereotyped, limb movements mainly of the lower extremities that occur during sleep [1]. PLMS appear to be genetically linked to restless leg syndrome (RLS) and a vast majority of patients (80–88%) with RLS concurrently have PLMS. However, the converse may not be true as PLMS are seen in individuals without RLS and are also observed in individuals with a variety of conditions such as obstructive sleep apnea (OSA), narcolepsy, rapid eye movement (REM) sleep behavior disorder, obesity, depression, fibromyalgia, and diabetes mellitus [2,3]. Similar to RLS, previous studies have shown a 5–8% prevalence of PLMS in the general population. The prevalence appears to increase with age and is likely related to the decrease in dopaminergic activity in the central nervous system [4–6]. Although the prevalence of PLMS increases with age, recent data suggest that the severity may not worsen with age [7]. There appears to be no gender-specific predilection to PLMS [8].

Emerging data suggest that PLMS is associated with an array of chronic medical conditions such as cardiovascular disease, chronic kidney disease, sleep apnea, Parkinson's disease, insomnia and depression [9–12]. Recent research has also focused on increased mortality in patients with congestive heart failure and end-stage renal disease when there is a concomitant diagnosis of PLMS. Specifically, a vast body of literature has been published in the last few years looking at the association between PLMS and cardiovascular disease. It has been postulated that arousals associated with PLMS may activate the sympathetic adrenergic system resulting in heart rate and blood pressure elevations [13,14], and thereby predisposing to adverse cardiovascular events [11,15]. This article critically reviews the currently available literature on the relationship between PLMS and cardiovascular disease outcomes.

## 2. Diagnosis

Unlike RLS which is a clinical diagnosis based on symptoms, signs, and clinical characteristics, a diagnosis of PLMS is based on the detection of movements during polysomnography (PSG) (Fig. 1). According to the International Classification of Sleep Disorders, 2nd Edition (ICSD-2), PLMS are scored on the PSG if each limb movement is: (i) 0.5–10 s in duration; (ii) electromyogram (EMG) amplitude increases to $\geqslant 8$ μV above the resting baseline;

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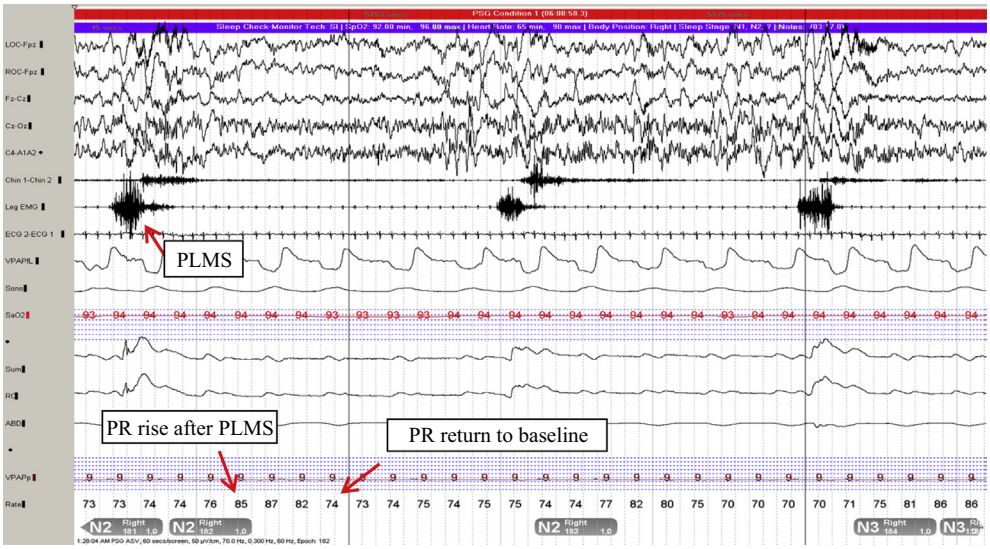


**Fig. 1.** Hypnogram with a 30 s epoch demonstrating periodic limb movements during sleep (PLMS) with associated increase in pulse rate and arousal. PR, pulse rate.

(iii) occurs in a sequence of four or more movements; and (iv) onset of consecutive movements are >5 s and <90 s apart. Periodic limb movement index (PLMI) is defined as >15 movements/h in adults and >5 movements/h in children [1,16,17]. When these PSG findings are associated with symptoms of sleep disturbance or a complaint of daytime fatigue that cannot be better explained by another sleep disorder, the condition is known as periodic limb movement disorder (PLMD) [1]. Though PLMS most commonly affects the muscles of the lower extremities, it can also affect the arm muscles [18]. EMG activity during PLMS can vary from tonic clonic to myoclonic jerks and can occur only in one leg or on one side of the body or alternate between the two sides [19,20].

## 3. Pathophysiology of PLMS

The pathophysiological mechanism of PLMS appears to be related to a complex neurologic process involving the dopaminergic system with origins in the brain stem and spinal cord leading to increased autonomic and motor activity [13]. This hypothesis is supported by the fact that drugs that are effective to treat RLS, and which act on the dopaminergic system, are also effective treatment options for most patients with PLMD [21]. In a study by Bucher et al. using functional MRI scans of individuals with PLMS, all the study participants were found to have bilateral cerebellar and red nucleus activation. Areas in the brain stem and pons were also noted to have activation suggesting the possibility of an involuntary mechanism of induction and a subcortical origin for PLMS [22]. Other studies have shown that PLMS are generated within the spinal cord from enhanced spinal cord excitability [23–26].

PLMS appear to occur in cyclical pattern every 20–40 s and predominantly during non-rapid eye movement (NREM) sleep. This observation also leads to the hypothesis that there could be a strong relationship between PLMS and the periodic neurological activity noticed on electroencephalogram (EEG) during NREM sleep known as cyclic alternating pattern (CAP). CAP is associated with increased autonomic activity, and the finding of higher frequency of PLMS during NREM sleep suggests the possibility of a common focus of origin [27]. Additionally, PLMS are more frequent at the beginning of the night (coinciding with NREM sleep stages) and decrease significantly during later sleep phases [28,29] (Fig. 2).

## 4. Clinical significance

Recent evidence demonstrating a strong genetic link of PLMS through the genes *BTBD9*, *GLO1* and *DNAH8* raises the possibility that there is biological plausibility for this condition [30]. However, there is controversy regarding the clinical significance of PLMS in the absence of RLS symptoms. Patients manifesting PLMS may have complaints of insomnia or daytime fatigue and sleepiness, which, if other sleep disorders are excluded, would give them a diagnosis of PLMD. Although the patient is typically not aware of these limb movements, patients' quality of sleep may be compromised and their bed partner might recognize them. Similarly, these movements might affect the bed partner's quality of sleep and might be the first indication that the patient has PLMS. PLMS can occur without associated EEG micro-arousals, and several studies have supported the argument that PLMS is not associated with daytime symptoms [31,32]. Also, if associated with micro-arousals, the frequency of PLMS does not appear to correlate with objective measures of daytime sleepiness or with indices of disrupted sleep [21]. Studies on the association between PLMS and insomnia (associated with frequent nocturnal arousals) did not find a strong correlation. Specifically, there was no correlation between PLMS and changes in sleep architecture [33] and absence of relationship between PLMS and mean sleep onset latency on MSLT [34]. A more recent study found a positive correlation between PLMS and subjective assessment of tiredness, total sleep time, sleep efficiency, physical fitness and psychological wellbeing [35]. Overall, the non-specific nature of the movements, occurring in association with a wide range of other disorders as well as in otherwise normal elderly people, raises questions as to whether they have any clinical significance of their own or are simply an epiphenomenon of other disorders [31,36,37]. However, more recent research has focused on the association between PLMS and increased risk of mortality in individuals with cardiovascular and renal disease [10,11,38].

## 5. Effect of PLMS on cardiovascular system

As described earlier, each movement of a PLMS cluster is associated with autonomic responses in the form of discrete elevations in blood pressure and heart rate (Fig. 1). Whether this will